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EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,014	ANSORGE ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-11,17,20,25,28,30 and 39-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-11,17,20,25,28,30 and 39-46* is/are rejected.

7)☒ Claim(s) *47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Remarks

1. Claims 1-7, 9-11, 17, 20, 25, 28, 30 and 39-47 are pending.

Claim Rejections - 35 USC § 112/101

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 20, 25, 28 and 30 recite a medicament or a pharmaceutical preparation method comprising utilizing alanyl aminopeptidase inhibitors to prepare a medicament or pharmaceutical preparation, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

4. Claims 20, 25, 28 and 30 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7, 9-11, 17, 20, 25, 28, 30, 39-43, 45 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

7. As stated in the previous office action, claims 1-7, 9-11, 17, 20, 25, 28, 30, 39-43 and 45 are rejected in part due to a lack of written description of the genus alanyl aminopeptidase inhibitors and methods of increasing TGF-β1 expression and treating and/or preventing autoimmune and inflammatory conditions using these inhibitors. Paragraph 0012 of the specification recites the following specific examples of alanyl aminopeptidase inhibitors: actinonin, leuhistin, phebestin, amastatin, bestatin, probestin, arphamenin, MR 387, thalidomide, PAQ-22 and RB3014. Paragraph 0012 of the specification also recites the following general classes of compounds as examples of alanyl aminopeptidase inhibitors: β-amino thiols, α-amino phosphonic acids and their esters and salts, α-amino phosphonates, α-amino boronic acids, α-amino aldehydes, hydroxamates of α-amino acids, N-phenyl phthalimides, N-phenyl

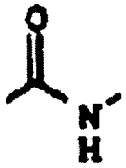
homophthalimides, α-ketoamides, thalidomide derivatives, and 3-amino-2-oxo-4-phenylbutanoic acid amides.

8. On pages 8 and 9 of the response filed 5/31/2007, Applicant argues that the skilled artisan would recognize that a common characteristic feature of these inhibitors is their affinity for the active site of alanyl aminopeptidase and specifically their ability to interact with active site residues E355, H388, E389, H392, E411 and Y477. Furthermore, Applicant argues that synthetic inhibitors such as β-amino thiols, α-aminoaldehydes, α-amino phosphonates,4-amino-L-prolines, and α-amino boronic acids, are characterized by the incorporation of zinc binding groups and P and/or P' side chains. Applicant provides the post-filing date reference Xu *et al.* to support these arguments.

9. The specification does not teach the partial structure or chemical/physical properties of compounds with an affinity for the active site of alanyl aminopeptidase and specifically an ability to interact with active site residues E355, H388, E389, H392, E411 and Y477. The specification does not teach chemical moieties that promote interactions with these active site residues or chemical moieties that are required for inhibitory activity. Absent this teaching the skilled artisan would not be able to envision the detailed chemical structure of β-amino thiols, α-amino phosphinic acids, α-amino phosphonates, α-amino boronic acids, α-amino aldehydes, hydroxamates of α-amino acids, N-phenyl phthalimides, N-phenyl homophthalimides, α-ketoamides, thalidomide derivatives, or 3-amino-2-oxo-4-phenylbutanoic acid amides with this ability. This is due in part to the sheer breadth of the claims. Because the specification fails to further define these subclasses, a broadest reasonable interpretation of the claimed genus

includes all compounds possessing the chemical moieties recited above. For example, the sub-genus β-amino thiols includes all compounds comprising the following chemical moiety:

Likewise, the sub-genus α-aminoaldehydes includes all compounds comprising the following chemical moiety:



An infinite number of compounds could contain these moieties. Absent evidence that these moieties are sufficient in any context to inhibit alanyl aminopeptidases, a complete description of the claimed genus must be lacking.

10. Regarding the reliance on Xu *et al.*, the requirement for written description set forth in 35 U.S.C. 112 pertains to what Applicant was in possession at the time the application was filed. On pages 290-294, Xu *et al.* teach examples of inhibitors that fall within each of the classes β-amino thiols, α-amino aldehydes, α-amino phosphonates,4-amino-L-prolines, and α-amino boronic acids, as well as general structural principles that can be used to envision the structure of alanyl aminopeptidase inhibitors. However, the reference has a post-filing publication date and therefore is not representative of the state of the art at the time of filing. In addition, because the specification does not explicitly define β-amino thiols, α-amino phosphinic acids, α-amino phosphonates, α-amino boronic acids, α-amino aldehydes, hydroxamates of α-amino acids, N-

phenyl phthalimides, N-phenyl homophthalimides, α-ketoamides, thalidomide derivatives, or 3-amino-2-oxo-4-phenylbutanoic acid amides, a broadest reasonable interpretation of the claimed genus includes all compounds possessing these moieties as stated for β-amino thiols and α-aminoaldehydes above. The claims are not limited to the compounds described in Xu *et al.* and in fact the claimed genus is significantly broader than the subgenus outlined in Xu *et al.* Therefore, claims 1-7, 9-11, 17, 20, 25, 28, 30, 39-43 and 45 stand rejected due to a lack of written description of the genus alanyl aminopeptidase inhibitors.

11. With respect to the arguments on pages 10 and 11 regarding PAQ-22, RB3014 and MR 387, the cited reference Bauvois *et al.* disclose in figure 2 a compound with a structure identical to that on page 10 of the response filed 5/31/2007 but with a name PIQ-22. The references cited in Bauvois *et al.* for this compound are prior art. Given the discrepancy between the name and the structure, the rejection with respect to PAQ-22 is maintained. Bauvois *et al.* also teach MR 387 (Figure 4). The references cited in Bauvois *et al.* for MR 387are also prior art. Therefore, the rejection with respect to MR 387 is withdrawn. Compound 39 of Bauvois *et al.* is a salt of the structure recited for RB3014 on page 11 of the response filed 5/31/2007. There is nothing in the Bauvois *et al.* reference to connect the name and structure. Therefore, the rejection is maintained with respect to RB3014.

12. As stated in the previous office action, claims 1-7, 9-11, 17, 20, 25, 28, 30, 39-43 and 45 are rejected in part due to a lack of written description of the genus inhibitors of enzymes that are similar to alanyl aminopeptidase. Paragraph 0015 of the specification states that the enzymes CD13, E.C. 3.4.11.2, cytosolic alanyl aminopeptidase, ZAAP, PSA and E.C. 3.4.11.14 each exhibit similar substrate specificity and inhibitor sensitivity. On pages 11 and 12 of the response

filed 5/31/2007, Applicant argues that the skilled artisan would recognize these enzymes by two conserved sequence elements, a zinc binding motif and an exopeptidase motif in the catalytic domain. This teaching is not included in the specification and the claims are not limited · inhibitors of enzymes with these structural features. Furthermore, the reference Albiston *et al.* is post-filing date art and therefore not representative of the state of the art at the time the invention was filed. On page 12, Applicant argues that bestatin is capable of inhibiting APN, PSA and LTA4H and that PAQ-22 is capable of inhibiting APN and PSA. This teaching is not found in the specification nor is it supported by a prior art reference. There is no evidence that the skilled artisan would be able to envision the detailed chemical structure of all inhibitors of all enzymes having a similar substrate specificity to alanyl aminopeptidase based on the description in the specification and the state of the art at the time of filing. Therefore, claims 1-7, 9-11, 17, 20, 25, 28, 30, 39-43 and 45 stand rejected in part due to a lack of written description of the genus inhibitor of enzymes that are similar to alanyl aminopeptidase.

13. Finally, as noted in the previous office action, the specification does the complete or partial structure of a peptide fragment of pathogenic autoantigens or synthetic analog and/or specific antigenic component of pathogenic microorganisms that would be useful for supplementing the alanyl aminopeptidase inhibitors in therapy. The relationship between the structure of such compounds and their claimed activity is not reported nor is a method for isolation. Applicant has not presented a response to this line of rejection.

14. Therefore, only phebestin, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath*

makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

15. Claims 1-7, 9-11, 17, 20, 25, 28, 30 and 39-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of phebestin to upregulate TGF-β1 and to treat lupus and arthritis, does not reasonably provide enablement for all other alanyl aminopeptidase inhibitors or for the treatment and/or prevention of all other autoimmune disorders, hay fever, allergies, asthma or graft versus host disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and are as follows:

(1) the nature of the invention

16. The invention is drawn to alanyl aminopeptidase inhibitors. Methods for upregulating TGF-β1, and treating and/or preventing autoimmune disorders, hay fever, allergies, asthma and graft versus host disease are also claimed.

(2) the state of the prior art

17. Ansorge *et al.* (WO 01/89569 cited on Information Disclosure Statement received 10/3/2006) teach pharmaceutical compositions comprising the alanyl aminopeptidase inhibitors actinonin, leuhistin, phebestin, amastatin, probestin, β-amino thiols, α-amino phosphinic acids, and α-amino phoshinic acid derivatives (see claim 10). The compositions are disclosed as being

useful for the treatment of autoimmune diseases and chronic diseases with an inflammatory genesis as well as for a treatment of rejection episodes after a transplantation (abstract). However, Ansorge *et al.* do not present data that demonstrate the function and effectiveness of these compounds but rather merely suggest a potential use for the compositions.

18. Andrulis (WO 95/04533 cited on the IDS filed 10/3/2006) teaches methods and pharmaceutical compositions for treating rheumatoid arthritis with thalidomide (abstract), an alanyl aminopeptidase inhibitor recited in the Markush Group of claims 41-43 of the instant application. Andrulis teaches that thalidomide is also used to treat acute and chronic graft versus host disease (page 2, lines 8 and 9). Thus Andrulis supports the use of alanyl aminopeptidase inhibitors to treat rheumatoid arthritis.

19. With the exception of thalidomide, alanyl aminopeptidase inhibitors are not known in the art for upregulating TGF-β or for treating autoimmune and inflammatory conditions.

20. Sharabi *et al.* (*PNAS*, **2006**, *103*, 8810-5) teach that a peptide based on the complementarity-determining region 1 of an autoantibody ameliorates lupus by upregulating TGF-β, suggesting that compounds that increase the level of TGF-β may suppress and treat an autoimmune disease such as lupus.

21. Youn *et al.* (*Clin. Exp. Immunol.*, **2002**, *129*, 232-9) teach that metallothionein, a low molecular weight protein, acts as an immunosuppressant by up-regulating TGF-β and is an effective treatment for collagen-induced arthritis in mice.

(3) the relative skill of those in the art

22. The relative skill of those in the art is high.

(4) the predictability or unpredictability of the art

23. On page 13 of the response filed 5/31/2007, Applicants argue that one skilled in the art would appreciate that the course of autoimmune diseases includes the activation and proliferation of autoreactive immune cells, in particular autoreactive T-lymphocytes, and a reduction in the ability of regulatory T-cells to suppress inflammation and immune response. Accordingly, Applicants claim to present a novel approach for activation of regulatory T-cells though an induction of the immunosuppressive agent TGF-β1.

24. As noted in the previous office action, Le *et al.* (*Int. Immunopharm.*, 2005, 5, 1771-82) discuss the unpredictability associated with using TGF-β as a pharmacological agent to treat autoimmune and inflammatory conditions: "TGF-β is an immunoregulatory cytokine. Despite its multiple roles in autoimmune and inflammatory processes, it has been experimentally deployed as a potential therapeutic agent to control autoimmune and chronic inflammatory diseases. TGF-β has been implicated as one of the key regulators of regulatory T cells that are crucial for maintaining balanced immune responses. Nevertheless, its over-production contributes to persistent inflammation, thus antagonists of TGF-β delivered locally break the cycle of leukocyte recruitment and subsequent fibrosis. On the other hand, systemic administration of TGF-β by injections of the protein or by gene transfer inhibits inflammatory pathogeneses. In addition, enhanced levels of circulating TGF-β appear to be instrumental during the development of oral tolerance and in immunosuppression caused by cyclosporine treatment. The multiplicity of actions of TGF-β and their virtually ubiquitous expression call for more rigorous investigation of their roles in health and disease states and more importantly, careful evaluation of the potential as immunopharmacological agents."

25. Le *et al.* discuss the role of TGF-β in asthma and airway diseases as being particularly unpredictable: "In asthmatic airways, TGF-β1 is an important fibrogenic and immunomodulatory factor that may cause structural changes. Inflammatory cells infiltrating bronchial mucosa, and structural cells of the airway wall including fibroblasts, epithelial, endothelial and smooth muscle cells all of which are TGF-β producers. These diverse cell types increase the levels of TGF-β as observed in bronchoalveolar lavage fluid from asthmatic patients. Elevated TGF-β has been implied in the remodeling of the airway wall, which is related to subepithelial fibrosis. Interestingly, *in vitro* as well as *in vivo* studies have documented dual roles of TGF-β in airway diseases, functioning either as a pro- or an anti-inflammatory cytokine on infiltrating inflammatory cells. These apparently contradictory results may well be the consequences of using different experimental conditions. More clear-cut conclusions concerning the effects of TGF-β may be obtainable from studies using systemic or conditional gene depletion approaches."

26. Applicant has not responded to the high level of unpredictability associated with using TGF-B to treat autoimmune diseases.

(5) the breadth of the claims

27. The claims are drawn to alanyl aminopeptidase inhibitors and inhibitors of all enzymes with a similar substrate specificity. The scope of the enzymes to which the claims pertain is not defined. The scope of potential inhibitor compounds is extremely broad and includes β-amino thiols, α-amino phosphinic acids and their esters and salts, α-amino phosphonats, α-amino boronic acids, α-amino aldehydes, hydroxamates of α-amino acids, N-phenyl phthalimides, N-phenyl homophthalimides, α-ketoamides, thalidomide derivatives, and 3-amino-2-oxo-4-

phenylbutanoic acid amides. In addition inhibitor genus includes D-Phe-γ[PO(OH)-CH_2]-Phe-Phe, PAQ-22, RB3014 and MR 387, compounds for which the structures are not disclosed. Finally, the methods for treatment and prevention encompass a broad range of diseases including rheumatoid arthritis, Lupus Erythematodes, multiple sclerosis, insuline dependent diabetes mellitus, Morbus Crohn, Colitis Ulcerosa, psoriasis, neurodermatosis, glomerulonephritis, interstitial nephritis, vasculitis, autoimmune diseases of the thyroid gland, autoimmune-hemolytic anemia or other chronic diseases having an inflammatory genesis, arteriosclerosis, asthma, allergies, hay fever and host versus graft disease. Each of these conditions have different patient populations, treatments, causes, and symptoms.

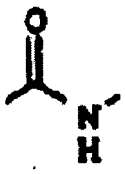
(6) the amount of direction or guidance presented; (7) the presence or absence of working examples

28. On pages 12 and 13 of the response filed 5/31/2007, Applicants note that the specification discloses assays for testing the ability of an alanyl aminopeptidase inhibitor to induce the expression of TGF-β1 and that phebestin, PAQ-22 and RB3014 are active. These data are not sufficient to enable the skilled artisan to practice the entire scope of the claimed invention for several reasons.

29. First, despite the availability of assays to identify alanyl peptidase inhibitors, the breadth of the genus presents an enormous burden on the skilled artisan to identify such compounds. The specification states that inhibitors may include β-amino thiols, α-amino phosphinic acids, α-amino phosphonates, α-amino boronic acids, α-amino aldehydes, hydroxamates of α-amino acids, N-phenyl phthalimides, N-phenyl homophthalimides, α-ketoamides, thalidomide derivatives, or 3-amino-2-oxo-4-phenylbutanoic acid amides with this ability. Because the

specification fails to further define these subclasses, a broadest reasonable interpretation of the claimed genus includes all compounds possessing the chemical moieties recited above. For example, the sub-genus β-amino thiols includes all compounds comprising the following chemical moiety:

Likewise, the sub-genus α-aminoaldehydes includes all compounds comprising the following chemical moiety:



An infinite number of compounds could contain these moieties. The specification provides no guidance to suggest that these moieties are sufficient in any context to inhibit alanyl aminopeptidases. In addition the specification provides no guidance to enable the skilled artisan to identify possible candidates for testing.

30. Second, the claims are also drawn to the administration of compounds that inhibit enzymes with similar substrate specificity to alanyl aminopeptidase. Paragraph 0015 of the specification states that the enzymes CD13, E.C. 3.4.11.2, cytosolic alanyl aminopeptidase, ZAAP, PSA and E.C. 3.4.11.14 each exhibit similar substrate specificity and inhibitor sensitivity. On pages 11 and 12 of the response filed 5/31/2007, Applicant argues that the skilled artisan would recognize these enzymes by two conserved sequence elements, a zinc binding motif and an exopeptidase motif in the catalytic domain. This teaching is not included in the

specification and the claims are not limited inhibitors of enzymes with these structural features. Furthermore, the reference Albiston *et al.* is post-filing date art and therefore not representative of the state of the art at the time the invention was filed. On page 12, Applicant argues that bestatin is capable of inhibiting APN, PSA and LTA4H and that PAQ-22 is capable of inhibiting APN and PSA. This teaching is not found in the specification nor is it supported by a prior art reference. Thus, there is no guidance in the specification or the prior art to enable the skilled artisan to identify inhibitors of all enzymes having a similar substrate specificity to alanyl aminopeptidase.

31. Third, even if the skilled artisan could identify a representative number of alanyl peptidase inhibitors and test them in the assays for TGF-β1 induction outlined in the specification, they would still have the high level of unpredictability associated with the use TGF-β1 to treat autoimmune disorders to contend with (see reference to Le *et al.* noted above). Neither the prior art or the specification provide guidance or working examples to illustrate that the full genus of autoimmune disorders can be treated by the upregulation of TGF-β1. Thus, the disclosed assays are relevant only to those disease states known in the prior art to be treatable by an upregulation of TGF-β, arthritis and lupus.

32. Finally, the specification does not provide structural information on "peptide fragments of pathogenic autoantigens or synthetic analogs and/or specific antigenic components of pathogenic microorganisms" that would be useful for supplementing the alanyl aminopeptidase inhibitors in therapy.

(8) the quantity of experimentation necessary

33. Considering the factors above, the skilled artisan would be burdened with undue experimentation in determining if a compound is an alanyl aminopeptidase inhibitor, if the compound can upregulate TGF-β1 in Treg cells and if the upregulation results in a treatment or prevention of autoimmune and inflammatory condition.

34. The rejection of claims 6, 7, 9, 10, 25, 28, and 39-42 under the enablement provision of 35 U.S.C. 112, first paragraph, for the term "prevention" is withdrawn in light of the amendment to the claims filed 5/31/2007.

35. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

36. Claims 1-4, 6, 7, 9-11, 17, 20, 25, 28, 30, 39-43 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

37. Claims 1-4, 6, 9-11 20, 25, 28, 30, and 39-43 recite the term "similar." The term "similar" is a relative term which renders the claim indefinite. The term "similar" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The use of the term "similar" renders the enzymes which can be inhibited by the claimed compositions and methods indefinite. Applicant has not responded to this line of rejection.

38. Claims 9, 10, and 28 recite the limitation "the type". There is insufficient antecedent basis for this limitation in the claim. Applicant has not responded to this line of rejection.

39. Claims 3, 5, 41-43 and 46 recite the limitations "PAQ-22", "RB3014" and "MR 387." Because no structure is disclosed for these chemical names in the specification, the claims are vague and indefinite. With respect to the arguments on pages 10 and 11 regarding PAQ-22, RB3014 and MR 387, the cited reference Bauvois *et al.* disclose in figure 2 a compound with a structure identical to that on page 10 of the response filed 5/31/2007 but with a name PIQ-22. The references cited in Bauvois *et al.* for this compound are prior art. Given the discrepancy between the name and the structure, the rejection with respect to PAQ-22 is maintained. Bauvois *et al.* also teach MR 387 (Figure 4). The references cited in Bauvois *et al.* for MR 387are also prior art. Therefore, the rejection with respect to MR 387 is withdrawn. Compound 39 of Bauvois *et al.* is a salt of the structure recited for RB3014 on page 11 of the response filed 5/31/2007. There is nothing in the Bauvois *et al.* reference to connect the name and structure. Therefore, the rejection is maintained with respect to RB3014.

40. The rejection of claim 7 for use of the phrase "for example" is withdrawn in light of the amendment to the claim filed 5/31/2007.

41. The rejection of claims 1 and 20 for the use of the phrase "introduction of the production of TGF-β1 and of the expression of TGF-β1 in and/or on Treg cells" is withdrawn in light of the amendment to the claim filed 5/31/2007.

42. The rejection of claims 1, 9 and 39 for use of the phrase "or of several inhibitors" is withdrawn in light of the amendment to the claim filed 5/31/2007

43. The following is a new ground of rejection. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Section 2173.05(h) of the MPEP states: "Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925)." Claim 3 uses the phrase "is selected form the group" twice and it is not clear which inhibitors are included in the scope of the claim.

Claim Rejections - 35 USC § 102

44. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

45. Claims 20, 25, 28, 30, 39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Ansorge *et al.* (WO 01/89569 cited on Information Disclosure Statement received 10/3/2006). Ansorge *et al.* teach pharmaceutical compositions comprising the alanyl aminopeptidase inhibitors actinonin, leuhistin, phebestin, amastatin, probestin, β-amino thiols, α-amino phosphinic acids, and α-amino phoshinic acid derivatives (see claim 10). The compositions are disclosed as being useful for the treatment of autoimmune diseases and chronic diseases with an

inflammatory genesis as well as for a treatment of rejection episodes after a transplantation (abstract).

46. In response to Applicant's argument that the reference does not teach that the compositions are for use in patients in need of induction of the production of TGF-b1 and of the expressionof TGF-B1 in and/or on regulatory T-cells, intended use or functional characteristics of a claimed composition are inherent properties of the composition. If the composition is physically the same, it must have the same functional properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) See MPEP § 2112.01. See MPEP § 2112.

47. The rejection of claims 1, 2, 4, 6, 7, 11, 20, 25, 28, 30, 39-41 and 43 under 35 U.S.C. 102(b) as being anticipated by Andrulis (WO 95/04533 cited on the IDS filed 10/3/2006) is withdrawn in light of the amendment to the claims filed 5/31/2007.

48. Claims 20, 25, 28, 30 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Ansorge et al. (U.S. Publication No. 2004/0147434). Ansorge et al. teach pharmaceutical compositions comprising the alanyl aminopeptidase inhibitors actinonin, probestin, phebestin, and leuhistin (paragraph 0014). As stated above, the intended use of the claimed compositions is an inherent property of the compositions taught by Ansorge et al. Applicant has not filed arguments in response to this rejection.

49. Claims 20, 25, 28, 30 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Ansorge et al. (U.S. Publication No. 2004/0132639). Ansorge et al. teach pharmaceutical

compositions comprising the alanyl aminopeptidase inhibitors actinonin, probestin, phebestin, and leuhistin (paragraph 0029). As stated above, the intended use of the claimed compositions is an inherent property of the compositions taught by Ansorge et al. Applicant has not filed arguments in response to this rejection.

50. Claims 20, 25, 28, 30 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Ansorge et al. (U.S. Publication No. 2005/0014699). Ansorge et al. teach pharmaceutical compositions comprising the alanyl aminopeptidase inhibitors actinonin, leuhistin, phebestin, amastatin, probestin, β-amino thiols, α-amino phosphinic acids, and α-amino phoshinic acid derivatives (claim 4). As stated above, the intended use of the claimed compositions is an inherent property of the compositions taught by Ansorge et al. Applicant has not filed arguments in response to this rejection.

51. Claims 20, 25, 28, 30 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Ansorge *et al.* (U.S. Publication No. 2006/0040850). Ansorge *et al.* teach pharmaceutical compositions comprising the alanyl aminopeptidase inhibitors actinonin, leuhistin, phebestin, amastatin, probestin, β-amino thiols, α-amino phosphinic acids, and α-amino phoshinic acid derivatives (claim 29). As stated above, the intended use of the claimed compositions is an inherent property of the compositions taught by Ansorge *et al.* Applicant has not filed arguments in response to this rejection.

52. The applied references for the rejections under 35 U.S.C. 102(e) above have a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not

claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Double Patenting

53. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

54. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

55. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

56. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-12 of copending Application No. 10/250,475. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant has not filed arguments in response to this rejection.

57. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 33-

45 of copending Application No. 10/250,476. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant has not filed arguments in response to this rejection.

58. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 10/296,102. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-13 and 20-30 of copending Application No. 10/296,102. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant has not filed arguments in response to this rejection.

59. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-22 and 32-42 of copending Application No. 10/507,548. Although the conflicting claims are not identical, they

are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant has not filed arguments in response to this rejection.

60. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 13 and 14 of copending Application No. 10/563,498. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-12 and 15-17 of copending Application No. 10/563,498. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant has not filed arguments in response to this rejection.

61. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 80-87 of copending Application No. 10/575,878. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising

inhibitors of alanyl aminopeptidase. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 78 and 79 of copending Application No. 10/575,878. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant has not filed arguments in response to this rejection.

62. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 79-89 of copending Application No. 10/575,882. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 77 and 78 of copending Application No. 10/575,882. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant has not filed arguments in response to this rejection.

63. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 80-86 of copending Application No. 10/575,883. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 78 and 79 of copending Application No. 10/575,883. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant has not filed arguments in response to this rejection.

Allowable Subject Matter

64. Claim 47 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

65. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.

66. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

67. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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